Altered Erythrocyte and Plasma Sodium and Potassium in Hypertension, a Facet of Hyperinsulinemia

HILLEL HALKIN, MICHAELA MODAN, MENACHEM SHEFI, AND SHLOMO ALMOG

SUMMARY Red blood cell sodium and potassium, plasma potassium, glucose and insulin responses to oral glucose load, serum urate, and plasma triglycerides were determined in a stratified subsample (n = 89) of a representative population sample (n = 1211), comprising 30 nonobese normotensive subjects with normal glucose tolerance (reference group) and 59 subjects representing each of the seven possible combinations of abnormal glucose tolerance, obesity, and hypertension. Rate of cation imbalance (red blood cell sodium > 7.0 mEq/L, potassium < 92.5 mEq/L, or plasma potassium > 4.5 mEq/L) was 88.1% in subjects with abnormal tolerance, obesity, or hypertension, as compared with 40.0% in the reference group (p < 0.001). These subjects were also characterized by significantly greater rates of insulin response: 60- and 120-minute postload levels of 100 mU/L or more (88.1 vs 46.7%), plasma triglycerides of 80 mg/dl or more (89.8 vs 53.3%) and serum uric acid of 5.5 mg/dl or more (61.0 vs 26.7%; p < 0.001 for all). The rate of cation imbalance was significantly associated with each of these three biochemical correlates: insulin response (p < 0.01), triglycerides (p < 0.001), and urate (p < 0.001). In the total population sample, the rate of untreated hypertension increased from 18% to 35% to 55.3% (p < 0.001), with an increase in the number of biochemical correlates of cation imbalance in combination with glucose intolerance and obesity. Since insulin is a regulator of membrane cation transport, whereas abnormal glucose tolerance, obesity, and hypertension, as well as elevated serum urate and triglycerides, are correlates of hyperinsulinemia and insulin resistance, we conclude that hyperinsulinemia is implicated in the cation transport abnormalities that characterize hypertension, obesity, and glucose intolerance. (Hypertension 11: 71-77, 1988)

KEY WORDS • hyperinsulinemia • red blood cell sodium and potassium • plasma potassium • serum uric acid • triglycerides • glucose intolerance • obesity • hypertension

HYPERTENSION, obesity, and the full spectrum of glucose intolerance (to be referred to here as the GOH conditions) are ubiquitously associated.1,6 Essential hypertension has recently been shown to be characterized by hyperinsulinemia, a long-known feature of obesity and glucose intolerance, where it reflects insulin resistance.6,11 Altered membrane cation transport is another feature shared by essential hypertension,12,13 obesity,14,15 and glucose intolerance.6,11 We have recently shown that the GOH conditions are characterized by similar shifts of red blood cell sodium and plasma potassium toward higher values and of red blood cell potassium toward lower values, a pattern that we termed internal cation imbalance.6 Since a considerable body of experimental evidence indicates that insulin is an important regulator of cellular membrane cation transport,11,17 we have suggested that hyperinsulinemia and insulin resistance are pathophysiological factors underlying the altered internal cation distribution that characterizes the GOH conditions.6

A third metabolic feature shared by the GOH conditions is the elevated serum uric acid level found in essential hypertension,18-20 obesity,21,22 and impaired glucose tolerance.19,23 We have recently demonstrated in a population study that elevated serum urate is a marker of hyperinsulinemia.24 Elevated triglyceride levels are an established marker of hyperinsulinemia and insulin resistance.25,26 Consequently, an associ-
ation of serum triglyceride and urate levels with internal cation imbalance would serve to confirm that the latter is a characteristic of hyperinsulinemia and insulin resistance.

To evaluate these possibilities, we analyzed the interrelationships of internal cation imbalance, as reflected by elevated red blood cell sodium, decreased red blood cell potassium, and elevated plasma potassium, with blood pressure, levels of insulin response to an oral glucose load, serum urate, and plasma triglycerides in a subset of a large representative sample of the adult Jewish population in Israel.

Subjects and Methods

Participants and Clinical Procedures
The current report addresses a subgroup of participants in the Israel Study of Glucose Intolerance, Obesity, and Hypertension (the Israel GOH Study). This is an ongoing nationwide longitudinal study of a population sample of 5711 persons born between 1912 and 1941 and first recruited in 1969. Full descriptions of sampling and follow-up, as well as of clinical and laboratory procedures, have been reported previously, and only details relevant to the present analysis will be described. Between 1979 and 1982, a representative group of the original population sample, consisting of 1211 participants (total study group) not known to be diabetic, attended regional medical centers after having weight, height, blood pressure, and regular use of medications (verified by inspection of drug receptacles) recorded at home. Blood pressure was measured with a standard mercury sphygmomanometer with subjects in the sitting position; four readings were obtained, two before and two after the interview. At the center a fasting venous blood sample was drawn for determination of glucose, uric acid, triglyceride, and creatinine concentrations, among other tests, followed by a 100-g oral glucose tolerance and insulin response test, with venous blood samples obtained at 60- and 120-minutes after glucose load.

Definitions
Relative weight was expressed as body mass index (BMI: weight/height² in kg/m²). Obesity was defined as a BMI of 25 or more. Most obese subjects were moderately obese; only 13.5% of the obese had a BMI of 31 or more.

Blood pressure categories were defined as follows:
1. Untreated hypertension: Subjects with at least two of four readings with systolic pressure exceeding 145 mm Hg or diastolic pressure exceeding 93 mm Hg. Most subjects had mild hypertension; only 6% had a diastolic blood pressure of 100 mm Hg or more.
2. Treated hypertension: Subjects who reported using any anti-hypertensive drug or diuretic.
3. Normotension: All remaining subjects.

Glucose tolerance was defined by the National Diabetes Data Group criteria as normal tolerance, abnormal tolerance (by combining the nondiagnostic and impaired glucose tolerance categories), and diabetes.

Selection of Cation Study Subsample
Participants not found to be diabetic by the oral glucose tolerance test were classified into a reference group (nonobese normotensive subjects with normal glucose tolerance) and seven diagnostic categories, representing all possible combinations of obesity, hypertension, and abnormal glucose tolerance. Lists of consecutive participants classified to each of the eight strata were compiled with the aim of selecting 30 subjects from the reference group and 70 subjects equally distributed among the other seven categories. These participants were asked to return to the regional center on a second occasion, at which time drug use was again ascertained and a fasting venous blood sample was obtained for determination of red blood cell and plasma sodium and potassium concentrations.

Laboratory Procedures
Plasma glucose, plasma triglycerides, serum creatinine, and serum uric acid levels were measured by routine automated Autoanalyzer II (Technicon Instruments, Tarrytown, NY, USA). Glucose measurement was based on potassium ferricyanide reduction. Uric acid was measured by the sodium tungstate method, creatinine by the picric acid method, and triglyceride levels by conversion to fluorophore. Plasma insulin was measured in duplicate by Phadebas radioimmunoassay (Pharmacia, Piscataway, NJ, USA). The within-assay coefficient of variation was 4%, and the between-assay coefficient was 8%. Insulin response was expressed as the sum of the 60- and 120-minute post-glucose load levels. Plasma and red blood cell cation concentrations, as markers of membrane cation transport activity, were determined by atomic absorption spectrophotometry. Ten milliliters of venous blood was drawn into a test tube containing one drop of calcium heparin, 25,000 U/ml. Plasma was separated and saved. The red blood cell layer was rapidly washed three times in ice-cold 140 mM choline chloride and centrifuged for 5 minutes at 3000 g. No electrolytes were detected in the final wash. Aliquots of the washed cells were drawn into capillary tubes and diluted 1:100 and 1:1000 with 3 μM lithium nitrate for measurement in duplicate of sodium and potassium levels, respectively, with a Perkin-Elmer atomic absorption spectrophotometer (Norwalk, CT, USA). Plasma aliquots were diluted 1:2000 and 1:100 in 3 M lithium nitrate and assayed in duplicate by the same method. Results are expressed as micromolar equivalents of cation per liter of packed red blood cells or plasma, respectively. Between-assay coefficients of variation for potassium at 5 and 100 mEq/L were 1.7% and 1.3% respectively, and for sodium at 7 and 140 mEq/L were 3.3 and 1.9%.

Data Analysis

Cation Study Subsample
The distributions of insulin response, serum uric acid, and plasma triglycerides in the reference and GOH groups were compared by Fisher’s exact test for 2 x 3 tables. Red blood cell sodium of 7.0 mEq/L or more, red blood cell potassium less than 92.5 mEq/L,
and plasma potassium of 4.5 mEq/L or more were termed markers of internal cation imbalance, which was defined as the presence of at least one marker. The association of the rate of internal cation imbalance with levels of insulin response, triglycerides, and urate was examined by chi-square analysis for linear trends. Comparison of the rate of internal cation imbalance between categories of various combinations of the GOH conditions and the reference group, between the sexes, and among combinations of elevated insulin response (≥100 mU/L), triglycerides (≥80 mg/dl), and urate (≥5.5 mg/dl) was done by Fisher’s exact test for 2×2 tables. Categorical analysis was chosen to enable direct comparison of the rates of specific combinations of the study variables as well as inclusion of extreme values in the analysis. Cutoff points for all the study variables were chosen to maximize discrimination between the reference and GOH groups.

**Total Study Group**

The association of all possible combinations of glucose intolerance, obesity, elevated insulin response, triglycerides, and urate with the prevalence of untreated hypertension was analyzed by chi-square test for linear trends in 1005 subjects of the total study group who were not receiving antihypertensive medications or diabetic.

**Results**

Of the 100 candidates selected for the cation study subsample, 89 participated, with 30 in the reference group. The GOH group comprised all 59 participants with any of the GOH conditions, alone or in combination, as follows: all three conditions, 13 subjects; abnormal tolerance, 7 subjects; obesity, 8 subjects; hypertension, 6 subjects; abnormal tolerance and obesity, 10 subjects; abnormal tolerance and hypertension, 4 subjects; obesity and hypertension, 11 subjects. Within the GOH group, 52 of 59 subjects (88.1%) had an internal cation imbalance, as compared with 12 of 30 subjects (40%) in the reference group (p<0.001). This rate was similarly high and significantly different from the reference group in all seven diagnostic categories, including abnormal glucose tolerance alone (Figure 1).

As expected, the GOH group, in comparison to the reference group, was characterized by distributions of insulin response, triglycerides, and uric acid that were significantly shifted toward higher values (Table 1), showing twofold greater proportions of insulin levels of 100 mU/L or more (88.1% vs 46.7%), triglyceride levels of 80 mg/dl or more (89.8% vs 53.3%), and uric acid levels of 5.5 mg/dl or more (61% vs 26.7%).

Rates of internal cation imbalance increased significantly with increasing insulin response in the total cation subsample (p<0.01), with a similar trend almost reaching statistical significance (p=0.08) within the reference group itself (Table 2). A highly significant positive association was also found between internal cation imbalance and triglycerides as well as uric acid (see Table 2) in both the total cation study subsample (p<0.001) and the reference group alone (p<0.001). Each of the three cation concentration ranges showed the same significant associations with urate, triglyceride, and insulin levels (data not shown). The presence of each of these three biochemical correlates of cation imbalance — insulin level of 100 mU/L or more, serum triglycerides of 80 mg/dl or more, and serum urate of 5.5 mg/dl or more — was associated with at least a twofold increase in the rate of cation imbalance compared to their absence.

The GOH group was significantly older than the reference group (43 of 59 were ≥50 years old [72.9%], whereas 15 of 30 reference group subjects were ≥50 years old [50.0%]; p<0.01), and the GOH groups within the total cation study subsample were ≥50 years old (50.0%; p<0.01) and the GOH group alone (p<0.001).

![Figure 1. Rate of internal cation imbalance in the reference group (R) and in the seven strata within the GOH group — abnormal glucose tolerance (G), obesity (O), and hypertension (H) alone — in all possible combinations. Numbers above bars denote significance level of the difference in rate in each stratum versus R. Numbers within bars indicate number of subjects.](image)

**Table 1. Distributions of the Biochemical Correlates Insulin Response, Triglycerides, and Serum Uric Acid in the Reference and GOH Groups Within the Total Cation Study Subsample**

<table>
<thead>
<tr>
<th>Biochemical correlate</th>
<th>Reference group (n=30)</th>
<th>GOH group (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin response (mU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>53.3 (16)</td>
<td>11.9 (7)</td>
</tr>
<tr>
<td>100-299</td>
<td>46.7 (14)</td>
<td>74.5 (44)</td>
</tr>
<tr>
<td>≥300</td>
<td>-</td>
<td>13.6 (8)</td>
</tr>
<tr>
<td>Total triglycerides (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>46.7 (14)</td>
<td>10.2 (6)</td>
</tr>
<tr>
<td>80-99</td>
<td>23.3 (7)</td>
<td>28.8 (16)</td>
</tr>
<tr>
<td>≥100</td>
<td>30.0 (9)</td>
<td>61.0 (34)</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>73.3 (22)</td>
<td>38.9 (23)</td>
</tr>
<tr>
<td>5.5-7.4</td>
<td>20.0 (6)</td>
<td>40.7 (24)</td>
</tr>
<tr>
<td>≥7.5</td>
<td>6.7 (2)</td>
<td>20.3 (12)</td>
</tr>
</tbody>
</table>

Triglycerides were determined in 56 of 59 GOH group subjects. Number of subjects is shown in parentheses. GOH = glucose intolerance, obesity, and hypertension. Dash indicates none in category.

*p<0.001 for the distribution of each of the three variables in the GOH group compared with the reference group.
Our findings demonstrate that internal cation imbalance, namely, increased red blood cell sodium and plasma potassium and decreased red blood cell potas-

<table>
<thead>
<tr>
<th>Table 2. Rates of Internal Cation Imbalance According to the Biochemical Correlates Insulin Response, Triglycerides, and Serum Uric Acid in the Total Cation Study Subsample and in the Reference Group Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical correlate</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Insulin response</strong></td>
</tr>
<tr>
<td>(mU/L)</td>
</tr>
<tr>
<td>&lt;100</td>
</tr>
<tr>
<td>100-299</td>
</tr>
<tr>
<td>≥300</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
</tr>
<tr>
<td>(mg/dl)</td>
</tr>
<tr>
<td>&lt;80</td>
</tr>
<tr>
<td>80-99</td>
</tr>
<tr>
<td>≥100</td>
</tr>
<tr>
<td><strong>Serum uric acid</strong></td>
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<tr>
<td>(mg/dl)</td>
</tr>
<tr>
<td>&lt;5.5</td>
</tr>
<tr>
<td>5.5-7.4</td>
</tr>
<tr>
<td>≥7.5</td>
</tr>
</tbody>
</table>

Dashes indicate none in relevant category.

*Significance levels for the increase in rate of cation imbalance in the total cation study subsample and reference group, respectively: insulin, p < 0.01, and p < 0.08; triglycerides and uric acid, all p levels < 0.001.

The group had a significantly greater preponderance of men (33 of 59 [55.9%] vs 11 of 30 [36.7%]; p = 0.01). Use of diuretics or antihypertensive medication, or both, was reported by 14 of 59 GOH subjects (23.7%) and by none of the reference group. Serum creatinine of 1.2 mg/dl or more was found in seven of 59 GOH group subjects (11.9%) and five of 30 reference group subjects (16.7%). Of these four factors, cation imbalance was significantly related only to sex (Table 3). In the GOH group, rates of cation imbalance were the same in both sexes (87.9 vs 88.5%). In the reference group, the rate of cation imbalance was lower than that in the GOH group in both sexes, but it was significantly higher in men than in women (72.7 vs 21.1%; p < 0.01). However, within the reference group, a zero rate of cation imbalance was observed in both sexes when all three biochemical correlates were absent; this rate was significantly lower (p < 0.01) than that in subjects with one or more of the correlates (Table 4). As this gradient of cation imbalance within the reference group was highly significant even for men alone (p < 0.01), the entire sex-related difference in rate of internal cation imbalance in the reference group resided in subjects with one or more correlates.

Thus, cation imbalance, apart from sex, was associated with three clinical correlates — hypertension, obesity, and abnormal glucose tolerance — as well as three biochemical correlates — insulin response of 100 mU/L or more, triglycerides of 80 mg/dl or more, and urate of 5.5 mg/dl or more.

To validate these findings, we examined the rate of hypertension, as related to all possible combinations of the other five clinical and biochemical correlates of cation imbalance in both sexes in the total study group, excluding diabetics and subjects receiving antihypertensive medications. This analysis revealed three strata with increasing risk for hypertension (Table 5): 1) presence of no more than one of the biochemical correlates, 18.0%; 2) glucose intolerance or obesity alone, or any combination of two or three of the five correlates, 35.0%; 3) any combination of four or five correlates, 55.3%. Within these strata there was no effect of obesity and no significant difference in the rates of hypertension related to specific combinations of these correlates (data not shown). Also, within the strata no significant differences were found between men and women. Women had significantly fewer correlates of cation imbalance, so that their total rate of hypertension was significantly lower.

**Discussion**

Our findings demonstrate that internal cation imbalance, namely, increased red blood cell sodium and plasma potassium and decreased red blood cell potas-
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TABLE 5. Rate of Hypertension in 1005 Nondiabetic Subjects of the Total Study Group Not Receiving Antihypertensive Medications by Sex and Combinations of the Clinical and Biochemical Correlates of Cation Imbalance

<table>
<thead>
<tr>
<th>No. of correlates</th>
<th>Total group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>60</td>
<td>17</td>
<td>43</td>
<td>20.9</td>
</tr>
<tr>
<td>One</td>
<td></td>
<td>18.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One biochemical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose intolerance or obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or three</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese</td>
<td>112</td>
<td>45</td>
<td>67</td>
<td>17.9</td>
</tr>
<tr>
<td>Obese</td>
<td>39</td>
<td>13</td>
<td>26</td>
<td>38.4</td>
</tr>
<tr>
<td>Four or five</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese</td>
<td>260</td>
<td>162</td>
<td>98</td>
<td>32.7</td>
</tr>
<tr>
<td>Obese</td>
<td>250</td>
<td>90</td>
<td>160</td>
<td>33.1</td>
</tr>
<tr>
<td>Total</td>
<td>1005</td>
<td>549</td>
<td>456</td>
<td>31.4</td>
</tr>
</tbody>
</table>

sium, is independently associated with hyperinsulinemia, in both the presence and absence of the GOH conditions. This finding is reinforced by the steep increase in the rate of hypertension with the increasing number of clinical (abnormal glucose tolerance and obesity) and biochemical correlates (elevated insulin response, plasma triglycerides, and serum uric acid) of cation imbalance found in the total study group.

Hypertension, obesity, and glucose intolerance are all independently characterized by hyperinsulinemia, which is known to be invariably attended by insulin resistance. A role for insulin in modulating cellular sodium and potassium membrane transport independent of glucose transport has been found in a variety of in vivo animal models. The effects of insulin on liver and muscle uptake of potassium in humans have been well defined. Whereas studies in diabetes have related mainly to potassium transport, studies in hypertension and obesity have concentrated mainly on the sodium ion, despite the inseparable linkage of cellular sodium influx and potassium efflux. Sodium transport mechanisms have been studied extensively in hypertensive and obese human subjects, and most studies have demonstrated a variety of abnormalities leading to increased intracellular sodium content. Recent studies in humans demonstrated insulin resistance of the Na⁺-K⁺ pump in adipocytes of obese subjects. The obvious inference is that, in hypertension, glucose intolerance, and obesity, the pattern of internal cation distribution is altered similarly, affecting cellular concentrations of sodium and potassium, as well as extracellular concentrations of potassium. Indeed, our data demonstrate these alterations in hypertension and in obesity independently of each other. In addition, abnormal glucose tolerance was also associated with internal cation imbalance when occurring alone, as well as when accompanied by the other two conditions; an observation subsequently reported in non-insulin-dependent diabetes mellitus as well.

These findings suggest that hyperinsulinemia and insulin resistance play a role in the internal cation imbalance that characterizes hypertension, obesity, and glucose intolerance. This contention is supported by the highly significant association between internal cation imbalance and elevated triglycerides and urate. Elevated triglycerides are a prominent characteristic of hyperinsulinemia and insulin resistance, which are accompanied by overproduction of very low density lipoproteins. An association of elevated triglycerides with altered cation transport mechanisms has recently been reported and hypothesized to reflect the effect of changes in plasma lipid levels on cellular membrane composition. Elevated serum uric acid level, another metabolic feature linking the GOH conditions, has recently been demonstrated to be a marker of hyperinsulinemia and insulin resistance in the large population sample from which the present study group was selected. The long-known association of increased triglyceride levels with elevated urate supports this finding.

To the best of our knowledge, a direct association between altered internal cation distribution and serum urate has not been described. Indirect evidence can be found in an earlier study in normal volunteers, in which the total plasma uric acid pool was found to correlate positively with total body potassium. The conclusion was that both total body potassium and urate pool were reflections of lean body mass. Since the latter is strongly correlated with insulin response and sensitivity, these findings are consistent both with elevated urate as a marker of hyperinsulinemia and insulin resistance and with its association with internal cation imbalance. Insulin has been shown to promote proximal renal tubular reabsorption of sodium, which under certain conditions decreases uric acid clearance and elevates serum urate. The association may also reflect a direct effect of hyperinsulinemia and insulin resistance leading to increased urate synthesis.

Similar to other studies, women in our reference group had a significantly lower rate of cation imbalance than men. This finding lends additional support to the link between insulin resistance and cation imbalance, since women have been reported to be more insulin-sensitive than men. Finally, in further support of this link, subjects with the combination of low levels of insulin response, triglycerides, and urate, all belonging to the reference group and in all likelihood
the most insulin-sensitive, presented a zero rate of cation imbalance. This was true even in men in the reference group, despite their overall excess internal cation imbalance. Moreover, in the total study group, the rate of hypertension was positively correlated with the number of these features of insulin sensitivity and cation imbalance that were present.

In summary, our findings in a population-based sample show that the internal cation imbalance and elevation of serum urate and triglycerides that characterize hypertension as well as glucose intolerance and obesity are significantly associated with the hyperinsulinemia that underlies these conditions. Moreover, the same associations are also present in persons free of the GOH conditions. These findings extend the implication of hyperinsulinemia and insulin resistance as pathophysiological mechanisms shared by hypertension, glucose intolerance, and obesity and suggest that internal cation imbalance may reflect hyperinsulinemia and insulin resistance. It remains to be seen whether this association is due to a direct role of insulin in the regulation of internal cation balance in humans or to other effects of hyperinsulinemia and insulin resistance.

Note added in proof: The insulin resistance that underlies essential hypertension has been confirmed recently by the euglycemic insulin-clamp technique. 

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